The Histopathology of Angiographic Chronic Total Coronary Artery Occlusions

Changes in Neovascular Pattern and Intimal Plaque Composition Associated with Progressive Occlusion Duration

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ABSTRACT: The current study describes the histopathology of angiographic chronic total occlusions including residual lumen patency, intimal plaque composition, patterns of neovascular channel formation, intimal plaque calcification, and cellular inflammation, analyzed according to occlusion duration and intimal plaque type (fibrocalcific vs. lipid laden vs. mixed). Histologic findings are related to previously described clinical and angiographic predictors of successful chronic total occlusion revascularization.

Key words: chronic total occlusion, calcification, atherosclerosis, angiogenesis, inflammation, collaterals, angioplasty, neovascular channels

In previously reported large series using conventional angioplasty technology, the initial and long-term success rates for revascularization of chronic total occlusions have been limited. Several clinical and angiographic factors associated with success or failure have been identified, and it is known that complications are frequent. The major problem facing the interventionalist is the inability to cross the occlusion with either a guide wire or the treatment device. The histologic basis for this inability to cross certain occlusions (particularly long standing occlusions) and the high incidence of long-term reocclusion or restenosis has not been defined.

Pathologic studies have provided some understanding of the histological basis for these problems with chronic total occlusion revascularization. We have examined our experience in a series of 64 patients with 99 angiographically documented chronic total occlusions undergoing autopsy evaluation. Coronary angiography was performed documenting chronic total occlusion within 3 months of death, and all patients had coronary angiography at our institution at least once and in the majority (95%) twice.

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demonstrating interim development of a chronic total occlusion in one or more coronary arteries. The last coronary angiogram was performed within 3 months of death in all cases. Acute plaque rupture cases with death resulting from thrombotic coronary occlusion were excluded. Total occlusion was defined in our study as a lesion with abrupt vessel cut-off (100% angiographic diameter narrowing), and either TIMI (Thrombolysis in Myocardial Infarction Trial) grade 0 or 1 antegrade flow distally.

**Histopathology**

This discussion will focus on the histopathology of total occlusions as it pertains to the percutaneous revascularization of these lesions. In our study,12 we used an ordinal grading system to evaluate the following composition of the intimal plaque (cholesterol, collagen, calcium, elastin, foam cells, giant cells, elastin, organized thrombus, intimal plaque hemorrhage), the patterns of neovascular channel formation, and the severity and type of cellular inflammation within the intima, media, and adventitia of chronic total occlusions. These histologic variables were analyzed in terms of both occlusion duration and predominant intimal plaque composition (fibrocalcific vs. lipid laden vs. mixed type). Recanalization score (the number of neovascular channels per high powered field) was determined in the following locations for the recanalized lumen, intimal plaque, media and the adventitia. We examined the relationship between neovascularization and cellular inflammation within the intimal plaque, media, and adventitia. There was a relatively even distribution of occlusions involving the right (43%), left anterior descending (30%) and circumflex (27%) arteries.12 The left main was occluded in just 2% of cases.

The estimated duration of occlusion was based upon the time from first observation of a subtotal lesion to chronic total occlusion progression in the same coronary segment on serial antemortem angiograms; or the time from an index event (myocardial infarction) to documentation of angiographic chronic total occlusion in the distribution appropriate for the prior MI. This period was added to the time between last angiography and autopsy to yield an estimate of lesion age. Since approximately 95% of these patients had serial angiograms, a reasonable estimate of the duration of the chronic total occlusion was obtained. Sixty-four percent of all total occlusions in this series were more than 1 year old, and greater than a third of all occlusions were more than 5-years-old (specifically; 19% of total occlusions were < 3 months, 17% between 3 months and 1 year, 29% between 1 and 5 years, and 35% greater than 5-years-old).

Using a histologic assessment of maximal lumen stenosis, it was evident that despite angiographic appearances, there were a substantial number of angiographic occlusions where the artery was subtotally occluded by histologic criteria. Indeed, only 22% of angiographic occlusions were totally occluded by histologic criteria. The rest were either 99% or subtotal stenoses. Twenty-five percent of these angiographic occlusions exhibited a lumen stenosis less than 95%. Thus, angiographically these lesions appeared chronically occluded, but histologically there was frequently a residual lumen. The presence of a residual lumen may facilitate guidewire passage and successful revascularization. No relationship was found between the degree of histologic lumen narrowing and the time from last angiography to death.
stenosis and either occlusion duration or intimal plaque composition.

Correlates of Occlusion Duration

Our study revealed the frequent occurrence of intimal plaque calcification even in total occlusions < 3 months old, and an increase in both the frequency and severity of intimal plaque calcification with advancing occlusion age. This age related increase in the calcium and collagen content of total occlusions may be the histologic basis for the observed difficulty in crossing and dilating lesions of advanced duration. Slightly less than two thirds of the chronic occlusions in our series (64%) were fibrocalcific, a quarter were mixed, and 11% were lipid laden. Figure 1A shows a typical fibrocalcific total occlusion estimated to be greater than 5 years in duration. A direct relationship was evident between increasing fibrocalcific content of the intimal plaque and the age of the total occlusion (Figures 2A, 3). Mixed intimal plaque composition decreased with time as lesions became harder or more fibrocalcific. Soft lipid laden lesions (Figure 1B) were infrequent, irrespective of the age of the chronic total occlusion, but predominated at younger occlusion ages (Figure 2B).

Figure 4 provides information relating the age of the total occlusion and cellular inflammation of the vessel wall. By evaluating the mean inflammation score according to vessel location, it is evident

Figure 2. (A) Cumulative frequency distribution curves for differing intimal plaque types as a continuous function of occlusion duration. Soft or lipid laden total occlusions predominate at younger occlusion ages while hard fibrocalcific lesions increase in frequency with advancing occlusion duration ($p=0.0003$). (B) Cumulative frequency distribution function curves for differing intimal plaque cholesterol categories as a continuous function of occlusion age. Intimal plaque cholesterol content is observed to increase with declining lesion age ($p=0.0007$). Reprinted with permission from Elsevier Science Publishing, Inc.12

Figure 3. Cumulative frequency distribution curves for intimal plaque calcium categories as a continuous function of occlusion age. Intimal plaque calcium content is observed to increase with advancing occlusion duration ($p=0.008$). Reprinted with permission from Elsevier Science Publishing, Inc.12
that the adventitia has significant levels of cellular inflammation very early on, but intimal plaque inflammation exceeds that found in either the adventitia or media across all total occlusion ages (Figure 4). Cellular inflammation is therefore an important component of chronic total occlusions especially lesions of younger duration. Intimal plaque erosions with overlying organized thrombus were evident in all lesion types, but were more frequent in younger total occlusions. Thus, intimal plaque erosions, lipid plaque components, organized thrombus and cellular inflammation are prominent early on in total occlusion development. Later on fibrocalcific changes predominate. This is the pathologic substrate for the temporal variation in success rates for revascularization seen with advancing duration of chronic total occlusion.

**Implications for Revascularization**

Prior literature has suggested that functional total occlusions, have higher success rates than true total occlusions. Concentric rings of organized thrombus and hemosiderin deposition were
evident within the intimal plaque of total occlusions in our study (Figure 5). These areas of hemosiderin deposition indicate areas of recurrent thrombus deposition and layered organization, leading to increasing plaque growth and lumen stenosis (Figure 5).

Within true total occlusions, small neovascularization channels were often seen traversing this loose organized tissue (Figure 6A). A small guide wire may potentially successfully traverse these recanalization channels. In practice, an 0.010 guide wire sometimes crosses a chronic total occlusion where other wires have failed presumably because it passes through a small lumen recanalization channel or intimal plaque neovascular channel (Figure 6B). Another recanalization route might be the relatively soft, centrally located area of amorphous tissue (Figure 6A), that may enable the operator to push through into the distal lumen with a stiffer guide wire.

Histologic patterns may have significant implications for both the choice of device technology utilized, and the success of percutaneous revascularization. Fibrocalcific deposits are frequent in total occlusions, and the pattern of calcification varies considerably. In older occlusions, calcification may be either circumferential or just a dense deposit in one quadrant of the intimal plaque (Figure 1A). This difference might have important consequences for the use of laser technology. Lasers are not effective at ablating calcium. Thus, concentric calcium deposition in a chronic total occlusion with predominantly fibrocalcific plaque, is not likely to be significantly impacted upon by a laser device. Alternatively, many chronic total occlusions have exuberant large adventitial neovascular channels (Figures 6C, 6D). A guide wire could be advanced through such a channel so that dilation within this neovascular channel might expand the outer components of the vessel wall.
Successful angioplasty treatment will depend also on the plaque composition, since the presence of large calcific deposits within the intimal plaque can interfere with the ability to dilate this region.

**Neovascularization**

A striking feature of all large total occlusion angioplasty series is the paucity of occlusion-site-related complications such as death, infarction, or need for emergency bypass surgery. This has been attributed to the protection afforded by well developed collateral flow. The present histologic study confirms extensive neovascularization in all vessel wall locations, irrespective of lesion age or stenosis severity (Figure 4). In occlusions <1 year old, the adventitia is the predominant vessel wall location of neovascular channel formation both in terms of number and size (Figure 6C). In occlusions >1 year old, intimal plaque capillary number and size increase to match those found in the adventitia (Figure 6B). Both intimal plaque and adventitial neovascular channel numbers remain greater, relative to the recanalized lumen (Figure 6A) or media across all occlusion ages. In our study, intimal plaque neovascular channels were observed to arise directly from the adventitial vasa vasora and were strongly correlated both anatomically and quantitatively with zones of cellular inflammation. Both the number and size of intimal plaque neovascular channels increased with progressive cellular inflammation of the intimal plaque.

Vasa vasorum and large adventitial neovascular channels (some traversing the media into the intimal plaque) are visible in Figure 6C. Adventitial passage of a guide wire through one of these channels is clearly feasible. We have inadvertently stented some adventitial channels without incurring vessel rupture which is a potential complication. Observations from the present study indicate that large neovascular channels (>250 μm diameter) were frequently present within the adventitia of total occlusions of all ages. The number of adventitial neovascular channels exceeded those found in all other vessel wall locations in occlusions greater than 1 year old, but with further growth, equivalent numbers of neovascular channels were observed in the adventitia and intimal plaque (Figure 4). These channels were connected with and derived from the adventitial vasa vasora. Since coronary collaterals less than 200μm in diameter are not clearly visualized by angiography, two conclusions may be inferred from these pathologic observations. First, angiographic bridging collaterals across total occlusions most likely represent enlarged neovascular channels arising from proliferated vasa vasorum within the adventitia. Second, the angiographic assessment of the antegrade collateral system of total occlusions is a poor indicator of the true microvascular collateral supply observed histologically in these lesions. This disparity in appearance between angiographic collaterals and histologic neovascular channels arises from vessel spasm, inadequate contrast filling of neovascular channels < 200 μm, as well as high distal coronary pressure that may limit antegrade flow within these collateral vessels. The role of the vasa vasorum and neovascular channels that grow from the adventitia into the intima-media remains speculative. Presumably, they function to nourish the occluded arterial segment. These vessels are thin-walled endothelial channels that may be sure to rupture, thereby leading to intra-plaque hemorrhage. In addition thrombotic occlusion or impairment of flow through these neovascular channels can augment plaque progression and contribute to medial necrosis and plaque rupture.

**Inflammation**

Cellular inflammation is greatest in younger lesions, particularly in the intimal plaque and adventitia. Prominent cellular inflammation involving lymphocytes, monocytes, and macrophages was frequently observed in all vessel wall locations in our study. The invariable colocalization of cellular inflammation and neovascularization within the intimal plaque and intimal plaque (IP) and media (M) of a total occlusion immediately adjacent to IP neovascular channels (asterisk). Reprinted with permission from Elsevier Science Publishing, Inc.
adventitia of total occlusions suggests that these processes may be closely related (Figure 7). Many growth stimulating and angiogenic factors are synthesized and released by cells in atherosclerotic arteries. This concept is supported by the fact that arterial vasa vasorum repairs after lipid and inflammatory cells are depleted by diet-induced layer of plasma cholesterol.22

This is also borne out by the observed association between increasing neovascular channel formation and progressive cellular inflammation of the intimal plaque. Whether cellular inflammation represents a cause or effect of neovascularization is unclear. Lymphocytes and monocyte-macrophages may play an active role in both angiogenesis and atherosclerotic lesion progression23,24 by producing a variety of mitogenic and angiogenic factors including basic fibroblast growth factor (bFGF), heparin binding epidermal growth factor-like factor, platelet-derived growth factor (PDGF), tumor necrosis factor a and transforming growth factor β.25,26 In atherosclerotic plaques, expression of the bFGF receptor (FGFR-1) is largely confined to the adventitial microvasculature suggesting a direct role for T lymphocytes and macrophage derived bFGF in adventitial neovascular growth.24 Stimulation of smooth muscle cell migration and proliferation by macrophage and T lymphocyte-derived PDGF and bFGF may also contribute to lesion progression.28 The neovascular channels of chronic total occlusions represent an attractive target for either mechanical or gene based local delivery of angiogenic factors. Enlargement and increase in the number or size of these neovascular channels over time in response to angiogenic stimulation could potentially obviate the need to open some of these total occlusions.

Conclusions

There are marked age-related changes in intimal plaque composition and neovascularization channel patterns of total occlusions. The adventitial and intimal plaque are the predominant zones of inflammation and neovascular channel formation. There is abundant cellular and angiogenic activity in the adventitia. The same is true of coronary restenosis. There is a close relationship between cellular inflammation and anatomic and quantitative neovascularization of total occlusions. What is the relevance of this type of histopathologic assessment to decision-making in interventional cardiology?

Undoubtedly, new devices will have to be effective against fibrocalcific lesions. That has important consequences for the use of laser technology. A technique that doesn’t cut calcium or severe fibrosis very well may be ineffective since total occlusions are fibrocalcific to a varying degree across all ages. Neovascularization is often prominent even in young lesions, and these neovascular channels may provide the basis for some novel approaches to enhance distal flow, such as the local delivery of potent angiogenic growth factors.

We have presented histologic data to suggest why angiogenic strategies might work. We may not need to pass a wire through or dilate recalcitrant fibrocalcific older lesions, if we could promote exuberant collateral growth around the lesion itself. Chronic total occlusion is indeed the mountain to be climbed for the practicing Interventionalist. As interventional cardiologists faced with revascularizing unyielding chronic total occlusions, we never know whether we just haven’t been trying hard enough. However, improved knowledge of the histopathology of these lesions, may allows us to evolve more effective treatment strategies in the future.

Summary of Findings

Over three quarters of all angiographic chronic total occlusions exhibit residual lumen patency (99% stenosis), despite angiographic documentation of total occlusion with distal TIMI 0 or 1 flow. In terms of composition, we find evidence of intimal plaque erosions with overlying and organized thrombus, and central lumen recanalization channels more commonly in younger total occlusions. Fibrocalcific intimal plaque content is more frequent in older chronic occlusions. Lipid accumulation is only seen in 10% of all total occlusions in our series, and decreases rapidly with increasing lesion age. Neovascular channels are most frequently seen in conjunction with cellular inflammation of the intimal plaque. The adventitia is extensively revascularized in chronic total occlusions of all ages. As with the intimal plaque, there is a close relationship between adventitial neovascular channels and adventitial cellular inflammation. The channels range in number and size from 150 μm to greater than 350 μm in diameter, so that one could eventually traverse some of these with a guide wire. These neovascular channels may represent a suitable target for local angiogenic drug delivery, which may obviate the need to open some of these chronic occlusions.
REFERENCES


